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# Effectiveness of a Single Dose of Oral Vs Rectal Paracetamol in Reducing Fever in Children Aged Between 2 to 6 Years – A Randomized Controlled Trial

**Nalaka Imbulana* and Lakkumar Fernando**
*District General Hospital, Gampaha, Sri Lanka*

## Abstract

**Background:** Rectal route of paracetamol is preferred to the commonly used oral route in some instances. Yet there is no previous documented study comparing the two routes in the local setting.

**Methods:** Single-centre, balanced randomized [1:1], two arms, parallel-group clinical trial was conducted in single Paediatric ward at the Gampaha District General Hospital, Sri Lanka. Children aged between 2-6 years with documented axillary temperature > 100° F were enrolled. Children were randomly divided into two arms with 135 participants in each arm. The first arm received single doses of 15 mg/kg oral paracetamol and second group received single doses of 30 mg/kg rectal paracetamol. A data extraction sheet was to record temperature at baseline and at 15 minutes, 30 minutes, 1 hour, 1 and1/2 hours, 2 hours, 2 and ½ hours and 3 hours after administration of the drug. The rate of temperature (time taken fever reduction by at least 1 F) reduction was calculated in 270 sample. In addition, the potential adverse events of the both groups were recorded.

**Results:** In the oral group, mean temperature reductions at 15 minutes, 30 minutes, 1 hour, 1 and1/2 hours, 2 hours, 2 and ½ hours and 3 hours after administration of the drug were 0.11, 0.44, 1.06, 1.68, 2.10, 3.18 and 2.75 0F respectively. The respective temperature reductions in rectal group were 0.26, 0.67, 1.31, 3.52, 2.81, 3.33 and 4.45 0F. When compared the means of both groups there was statistically significant difference between two groups in all the time periods ($P<0.05$) except at 1 hour after administration of paracetamol ($P = 0.06$). There was no statistical significant difference in side effects when comparing two arms as well.

**Conclusion:** A single dose of 30 mg/kg rectal paracetamol is more effective than single dose of 15 mg/kg oral paracetamol in reducing fever. There is no difference in relation to the safety of the two routes.

**Trial registration:** SLCTR, SLCTR/2017/025. Registered 17 August 2017-Retrospectively registered, https://slctr.lk/ SLCTR/2017/025

**Keywords:** Paracetamol; Oral; Rectal; Temperature; Fever

## Abbreviations

PCM: Paracetamol

## Introduction

Fever has become one of the most common clinical symptoms managed by the paediatricians and health care providers today. It is usually a natural reaction to infection. However, some other factors can raise the body temperature as well. In management of fever, clinicians commonly advice on temperature control via the use of over-the-counter antipyretics [1].

When children get fever, parents usually suffer from "fever phobia" [2,3]. Fever phobia is exaggerated fear of parents whose child have fever. It's actually a misconception of parents that fear is not dependent on socio-economic status of parents [4]. Most of the parents think that with high fever child can get serious neurological complications [5]. Parents are very much concerned to maintain normal temperature in their ill child.

Paracetamol is the most widely used drug for reducing fever in children [1,6]. It is safe in standard doses of 60 mg/kg/day and could be used either rectally or orally. [1,6,7,8] Though the oral route is the most commonly used, in some circumstances, the rectal route is preferred. Examples include; a child with febrile convulsion, fever with repeated vomiting, and high-grade fever without tolerating oral medication. It has been shown that oral paracetamol is absorbed within 30 to 60 minutes of ingestion. Pharmacokinetic properties of single dose of oral paracetamol are well studied. Nevertheless, pharmacokinetics of paracetamol when administered via rectal route is not well established. Its absorption is prolonged and depends on the size of suppository, base composition, and rate of dissolution. Moreover, some evidence has revealed that antipyresis serum concentration of 15 – 20 microgram/ml could not be achieved by rectal dose of 10 – 15 mg/kg and a rectal dose of 30 - 45 mg/ kg is needed [9,10].

Although several studies have been done, it has not been absolutely documented whether equal dose of rectal and oral paracetamol have similar effectiveness in reducing fever. Results of published studies comparing the effectiveness of these two preparations are not uniform.

Some shows oral administration of paracetamol was more effective than the rectal format, whereas other researchers reported that both have similar effectiveness. [1, 8,11,12,13,14] A meta-analysis shows that

***Corresponding author:** Nalaka Sanjeewa Imbulana, District General Hospital, Mihidu Mawatha, Gampaha, Sri Lanka, Tel: +94715783854, Email: nalakaib@gmail.com

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there is no difference in effectiveness of temperature reduction between oral and rectal paracetamol [15]. The widely used standard anti-pyretic dose of oral paracetamol is 15mg/kg/dose [19]. The standard anti-pyretic dose of rectal paracetamol is 30mg/kg as a single dose and then 15- 20 mg/kg every 4-6 hours as necessary [16]. This is the first ever clinical trial to compare the effectiveness of oral vs rectal paracetamol in reducing fever in the South Asian region according to literature.

Aim of this study was to compare the antipyretic effectiveness (rate of temperature reduction) and the side effects of single dose of 15mg/kg paracetamol given orally with that of 30 mg/kg given rectally in children aged 2-6 years and the null hypothesis of the study was that there would be no statistically significant difference in the antipyretic effectiveness between oral paracetamol given at 15 mg/kg and rectal PCM given at 30 mg/kg.

## Methods

### Trial design

Single centre, balanced randomized [1:1], single blind, two arms, parallel-group clinical trial was conducted to compare the antipyretic effectiveness and side effects of single dose of oral and rectal paracetamol.

### Participants

Children aged between 2-6 years admitted to the Paediatric Unit at the District General Hospital Gampaha were enrolled between June 2017 to December 2017. Eligibility criteria for study inclusion were: Children aged between 2-6 years; Duration of fever for a maximum of 3 days irrespective of the cause of fever and irrespective of prior administration of any anti-pyretic or any other medicines; Documented axillary temperature > 100° F at the time of recruitment. Exclusion criteria were: Children with known allergy to paracetamol; Conditions that preclude oral (example: vomiting) and rectal (example: diarrhoea) administration of medicines; Children with reduced level of consciousness; Children who had possible overdose of paracetamol; Children who had any anti pyretic within 8 hours of admission.

### Interventions

Children meeting inclusion and exclusion criteria and whose parents provided the consent, were allocated into two study arms using simple randomization. Arm 1: Single dose of paracetamol syrup 15mg/kg was given orally. The same preparation (syrup containing 120 mg/5ml of paracetamol) available in the Hospital Pharmacy was used throughout the study. The dose was calculated in mg and then converted to ml. The required dose was given by a calibrated sterile syringe. Arm 2: Single dose of paracetamol suppository 30 mg/kg was given rectally. The same preparation was used throughout the study. Rectal paracetamol is available as 125 mg, 250 mg, 500 mg suppositories, it was used in suppository form. As partition of the suppository to pieces was difficult, round up method was used. After allocation of children into each group, the recommended dose of Paracetamol was given. Dose was calculated to the weight. Therefore, before administration of drug weight of all the participants were measured by accurate digital weighing scale throughout the study. The intervention was administered by trained nurses and the outcomes was assessed by the principal investigator who was made unaware of the interventional status.

### Temperature measurements

Principal investigator who was blind to identity of the intervention, measured the temperature once before the administration of paracetamol and also in 15, 30, 60, 90, 120,150,180 minutes 'time after the administration of paracetamol. Same thermometer was used for the entire study. Principal investigator followed the standard protocol in measuring the temperature and recorded the readings in the questionnaire. Tepid sponging was not given by care givers during trial duration three hours as it may contribute to temperature reduction and can unduly influence the research outcome.

### Outcomes

**Primary outcome:** Time taken to fever reduction by at least 1°F (rate of temperature reduction) **Secondary outcome:** Maximum antipyresis following administration of single dose of Paracetamol within 3 hours' time.

### Sample size

135 participants were recruited into each group.

Formula of calculating sample size for detecting clinical superiority: $n = [(Z\ \alpha/2 + Z\ \beta)^2 \times \{2(ó)^2\}]/ (\mu1 - \mu2)^2$ [17,18]

n = sample size required in each group,

μ1 = mean change in intervention group = 2 μ2 = mean change in the control group = 1.7 μ1-μ2 = clinically significant difference = 0.3 ó = standard deviation = 0.84

Z α/2: The SND value corresponding to 5% significance level, taken as 1.96 Z β: The SND value of the Type II error when power is 80%, taken as 0.84

$$= 2\ (1.96 + 0.84)\ 2 \times 0.84^2$$

$$0.3^2$$

$$= \frac{2 \times 7.84 \times 0.7}{0.09}$$

= 121

Assuming a response rate of 90% N= 121/ 0.9 = 134 per each arm

### Randomisation and blinding

Block randomization was done using a computer-generated random letter sequence. A Co - investigator and the parents of the children were aware about the route of the drug given. But the principal investigator who is recording the temperature was blinded for the intervention.

### Statistical methods

Data analysis was done using Statistical Package for Social Sciences (SPSS) software version 21. Univariate analysis was performed using Chi Square test to compare categorical variables and independent samples t- test and one-way ANOVA were used to compare means between categories. Pearson correlation coefficient was used to determine correlations. Multivariate analysis was done using multiple logistic regression models. p value of $< 0.05$ was considered as statistically significant.

## Results

The study sample consisted of 270 children who were having fever more than 100 $^0$F. They were divided into two arms by block randomization and each arm consisted of 135 children. The first arm received a single dose of oral paracetamol and second arm received a

single dose of rectal paracetamol.

In the oral-paracetamol arm, mean participants' age was 4.07 years (SD – 1.414) and in the second arm, mean participant age was 3.4 years (SD – 1.205). When comparing the two means there was a statistically significant difference between two means. (P<0.05) In the first arm, 49.6% of the participants were males and in the second arm, 42.2% of the participants were males. The mean temperatures of both arms at 15 minutes, 30 minutes, 1 hour, 1 and ½ hours, 2 hours, 2 and ½ hours and 3 hours are demonstrated in Figure 1.

This shows that the mean temperature of the rectal group is higher than the oral group at the beginning of the study. With time the temperature has reduced more in the rectal group.

The mean temperature reduction at 15 minutes, 30 minutes, 1 hour, 1 and1/2 hours, 2 hours, 2 and

½ hours and 3 hours in both groups are as follows **(Table 1)**

When comparing the means of both groups there is a statistically significant difference between the two groups in all time periods except at 1 hour after administration of paracetamol. Therefore, null hypothesis was rejected in all the measured time periods except at 1 hour after giving paracetamol. **(Table 2)**

In the oral group mean time taken to reduce temperature by 1 $^0$F was 71.5 minutes. In the rectal group, mean time taken to reduce temperature by 1 $^0$F was 50.5 minutes. When comparing both means the P value was <0.001. Therefore, there is a statistically significant difference in time taken to reduce temperature by 1 $^0$F.

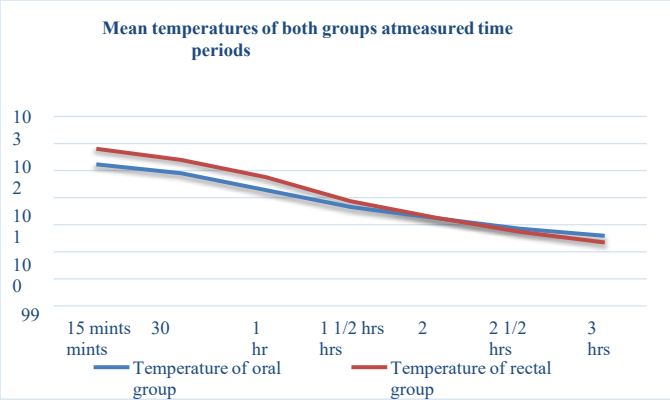


**Figure 1:** Comparison of mean temperatures of both groups at measured time periods.

When comparing the side effects of oral vs rectal group, no child develops flushing and skin rashes. In both groups only, few children developed hypothermia (Temperature less than 97.7 $^0$F). **(Table 3).**

At each measured time period P value is > 0.05, therefore there is no statistical significant difference in development of hypothermia in both oral and rectal groups.

## Discussion

In this study showed that there was a statistically significant difference in mean temperature reduction at 15 minutes, 30 minutes, 1 ½ hours, 2 hours, 2 ½ hours and 3-hour time periods (P < 0.05) when comparing between oral and rectal group. There was no statistically significant difference at 1-hour (P > 0.05). Therefore, according to my clinical trial 30 mg/kg rectal paracetamol is significantly more effective in reducing fever than 15 mg/kg oral paracetamol.

There was no statistical significant difference in side effects when comparing two arms as well. (all the P values measured in respective time periods were > 0.05)

In this randomized single blinded clinical trial, we compared temperature reduction after giving a single dose of 15 mg/kg oral paracetamol to one group with the other group receiving a single dose of 30 mg/kg rectal paracetamol. The drug was given after measuring the initial temperature. Following administration of the drug the temperature was measured at 15 minutes, 30 minutes, 1 hour, 1 ½ hours, 2 hours, 2 ½ hours and 3-hour time periods.

In each group mean temperature reductions at each time periods were calculated. The mean temperature reduction in all time periods were higher in the rectal group than the oral group. The findings we obtained from our clinical trial were different to the findings of most of the other studies conducted in other countries. A research done in 1977 using 10 mg/kg dose of both oral and rectal paracetamol in 30 children has shown that oral paracetamol is significantly better than rectal paracetamol in reducing fever. [8] But this study was not randomized, and they have used a low dose of paracetamol which is not the currently recommended dose. [16] According to the statistical formula we used the minimal sample required was 134 for each group. Hence, we included 135 participants for each group whereas their sample size was 30, which was quite small.

A study done in 2002 to compare the effectiveness of oral versus

**Table 1:** Mean temperature reduction at measured time.

| | 15 mints | 30 mints | 1 hour | 1½ hours | 2 hours | 2½ hours | 3 hours |
|---|---|---|---|---|---|---|---|
| **Oral Group** | .1126 | .4415 | 1.0667 | 1.6837 | 2.1015 | 2.4941 | 2.7474 |
| **Rectal Group** | .2644 | .6733 | 1.3119 | 2.1956 | 2.8185 | 3.3296 | 3.7289 |

**Table 2:** Comparison of mean temperature reduction.

| | 15 mints | 30 mints | 1 hour | 1½ hours | 2 hours | 2½ hours | 3 hours |
|---|---|---|---|---|---|---|---|
| **P Value** | 0.01 | 0.005 | 0.062 | ≤0.001 | ≤0.001 | ≤0.001 | ≤0.001 |
| **Null Hypothesis** | Rejected | Rejected | Retained | Rejected | Rejected | Rejected | Rejected |

**Table 3:** Number of children who developed hypothermia.

| | 15 mints | 30 mints | 1 hour | 1½ hours | 2 hours | 2½ hours | 3 hours |
|---|---|---|---|---|---|---|---|
| **Oral group** | 0 | 0 | 2 | 2 | 4 | 8 | 11 |
| **Rectal group** | 1 | 1 | 5 | 7 | 11 | 7 | 12 |
| **P Value** | .316 | .316 | .251 | .090 | .063 | .790 | .827 |

normal and high dose rectal paracetamol in the treatment of febrile children, conducted by Scolnik D et al, demonstrated that there was no difference in temperature reduction in patients treated with 15 mg/kg oral paracetamol and the same or double dose rectally. Even in this study the sample size was not satisfactory, and they had recruited 23, 23 and 24 children to each group. It is not a blind study as well. Another randomized, double-dummy, double-blind study of 51 febrile children, receiving one of three regimens of a single paracetamol dose of 15 mg/kg orally and 15 mg/kg rectally, or 35 mg/kg rectally revealed that they have similar antipyretic effectiveness. [12] Even though this is a double- blind study, there were only 16 – 18 participants in each group. Moreover, there was a wide age range of 6 months to 13 years in participants as well.

A meta-analysis done in 2008 by Lee Hilary Goldstein et al, revealed that there was no difference in oral and rectal paracetamol in fever reduction. [15] A research done to find out the effectiveness of rectal paracetamol in small children with fever in 1979 using 37 febrile children aged between 3 months to 6 years also showed that both have equal antipyretic effectiveness. [13] A study done by Hopkins CS, Underhill S, Booker PD et al, to evaluate the pharmacokinetics of paracetamol after cardiac surgery using 28 febrile children aged between 9 days to 7 years also demonstrated that there was no difference in antipyretic effect between the two routes of administration. [14]

According to the literature, there was only one study which had somewhat similar findings to our study. That was a randomized controlled trial conducted by Chomchai et al in a paediatric acute care setting on 2015 in Bangkok, Thailand. It revealed using rectal paracetamol in an acute situation with tepid sponging, can effectively reduce fever and keep body temperature down longer than oral paracetamol. [19] In this study, the sample size was 200, which is much higher in number when compared with all the above-mentioned studies.

Limitations of the study were: we conducted a single blinded trial where only the principal investigator was unaware about the treatment modality. If we conducted a double blinded trial, the findings would have been much more accurate. There was also a significant difference in mean age between two arms though the allocation was randomized. However, the impact of this on temperature reduction was unclear. In addition, we conducted this study in children aged between 2-6 years only and effects of oral and rectal paracetamol in fever reduction in neonates, infants, children aged between 1-2 years and children over 6 years were not assessed. Therefore, further research will be necessary to evaluate the antipyretic effectiveness in these age groups.

## Conclusion

A single dose of 30 mg/kg rectal paracetamol is more effective than a single dose of 15 mg/kg oral paracetamol in reducing fever. Occurrence of adverse events is seemingly similar in both groups. Therefore, we recommend rectal paracetamol over oral paracetamol for fever control in children especially when oral drugs are not tolerated and in acute paediatric settings like febrile status epilepticus where administration of oral paracetamol is difficult.

## Declaration

### Ethical approval and consent to participate

This study was approved by Ethical Review Committee of Faculty of Medicine, University of Kelaniya (Reference Number: P/103/03/2017). The trial was registered in Sri Lanka Clinical Trial Registry (SLCTR/2017/025). The study was performed after the parents of participants were fully informed. All the parents of the participants and signed an informed consent form and received written and verbal information before participating in this study.

### Consent for publication

Not applicable.

### Availability of data and materials

All data or analysed during this study are included in this published article.

### Competing interests

The authors declare that they have no competing interests.

### Funding Source

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### Authors' contributions

NI & LF designed and coordinated the implementation of the study. NI was responsible for data acquisition and drafted the manuscript. All authors reviewed and revised the manuscript, providing important intellectual content, and approved final version.

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The presentation of the manuscript is in Research Square. [20]

### Consort guidelines

The study adheres to the CONSORT (CONsolidated Standards of Reporting Trials) 2010 guideline.

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